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Health Effects Assessment for Tetrachloroethylene

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with tetrachloroethylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Tetrachloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-073. NTIS PB81-117830.

U.S. EPA. 1982. Hazard Profile for Tetrachloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983. Reportable Quantity Document for 1,1,2,2-Tetrachloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-82-005F. NTIS PB85-249704.

U.S. EPA. 1986a. Updated Carcinogenicity Assessment for Tetrachloroethylene (Perchloroethylene, PERC, PCE): Addendum to the Health Assessment Document for Tetrachloroethylene. Office of Health and Environmental Assessment, Washington, DC. NTIS PB86-174489.

U.S. EPA. 1987. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for tetrachloroethylene. On line. (Verification date 9/87; data input pending). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

A major issue of concern is the potential carcinogenicity of tetrachloroethylene to humans. Human data are confounded by composite exposures. Results of *in vitro* mutagenicity bioassays are inconclusive. Only one animal bioassay employing oral exposure has been conducted. Results in rats were negative. In mice, tetrachloroethylene administration resulted in an increased incidence of hepatocellular carcinoma. Using these data, a q_1^* of 5.1×10^{-2} $(mg/kg/day)^{-1}$ was estimated.

NTP (1986) conducted 2-year inhalation studies with mice and rats. Tetrachloroethylene exposure was associated with increased incidences of mononuclear cell leukemia in rats and liver tumors in mice. U.S. EPA (1986a) estimated unit risks of 2.9×10^{-7} to 9.5×10^{-7} for exposure to 1 $\mu g/m^3$ in air. The weight of the evidence for the carcinogenicity of tetrachloroethylene is proposed as Group B2, probable human carcinogen. The classification is currently under review prior to finalization.

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EEG	Electroencephalogram
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SNARL	Suggested no-adverse-response level
STEL	Short-term exposure limit
TCA	Trichloroacetic acid
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of tetrachloroethylene (CAS No. 127-18-4) are as follows:

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	165.83
Vapor pressure:	17.8 mm Hg at 25°C (U.S. EPA, 1982)
Water solubility:	150 mg/ℓ at 25°C (Keil, 1979)
Log K_{ow}:	3.40 (Hansch and Leo, 1985)
Soil mobility:	2.5 (Wilson et al., 1981) (predicted as the ratio of water velocity to compound velocity through a soil containing 0.087% organic carbon)
K_{oc}:	46 (Sabljic, 1984)
BCF:	49 (in bluegill, Lepomis macrochirus) (U.S. EPA, 1980a)
	39 (in rainbow trout, Salmo gairdneri) (U.S. EPA, 1980a)
Half-life in Air:	47 days (U.S. EPA, 1982)
Half-lives in Water:	12-25 days in coastal seawater (Wakeham et al., 1983) 3-30 days in river and 30-300 days in lake and groundwater (Zoeteman et al., 1980)

The primary removal mechanism for tetrachloroethylene in the atmosphere is expected to be reaction with photochemically generated hydroxyl radicals (U.S. EPA, 1985a). The principal product of this reaction is trichloroacetylchloride (U.S. EPA, 1979). The half-life value given above is estimated on the basis of tropospheric OH concentration of 10^6 radicals/cm^3.

Because of its relatively long half-life in the atmosphere, tetrachloroethylene may be transported long distances from its emission sources, but insignificant amounts will be transported from the troposphere to the stratosphere.

The primary removal mechanism for tetrachloroethylene in water will be volatilization. Bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments are not expected to be important fate processes (NLM, 1987).

The half-life of tetrachloroethylene in soil could not be located in the available literature. Tetrachloroethylene is expected to volatilize rapidly from soil surfaces. The half-life for evaporation from soil should be longer than its evaporation half-life from water (Wilson et al., 1981). In subsurface soil, no significant degradation is expected to occur under aerobic conditions; however, biodegradation may be an important process in anaerobic soils (NLM, 1987). Because of its relatively low K_{oc} value, tetrachloroethylene is expected to be quite mobile in soil and undegraded residue is expected to leach into groundwater. Detection of this compound in a number of groundwater supplies supports this prediction (NLM, 1987).

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

2.1. ORAL

Tetrachloroethylene is absorbed to some extent from the gastrointestinal tract (quantification and species not specified) (von Oettingen, 1964). Intestinal absorption by dogs is facilitated by fats and oils (Lamson et al., 1929).

Daniel (1963) found that 98% of a single oral dose of ^{36}Cl-tetrachloroethylene was eliminated in expired air and 2% in urine of rats. Schumann et al. (1980) reported that 85% of a single oral dose of 500 mg/kg ^{14}C-tetrachloroethylene was eliminated in expired air and 12% in urine of mice. These two studies indicate that tetrachloroethylene was almost completely absorbed from the gastrointestinal tract.

2.2. INHALATION

The principal route by which tetrachloroethylene enters the human body is by pulmonary absorption from the alveolar air (U.S. EPA, 1985a). Pulmonary absorption of tetrachloroethylene is rapid, and the amount of tetrachloroethylene absorbed at a given vapor concentration (for exposures of <8 hours) is directly related to the respiratory minute volume (Hake and Stewart, 1977). von Oettingen (1964) also reported that tetrachloroethylene is readily absorbed through the lungs (quantification and species not specified). Monster et al. (1979) found that tetrachloroethylene uptake by humans was influenced more by lean body mass than by respiratory minute volume or adipose tissue. The amount of metabolite produced is influenced primarily by metabolic rate constants. Since many of the effects of tetrachloroethylene are attributable to its metabolites, both update and metabolism are important variables.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Hayes et al. (1986) administered nominal doses of 0, 15, 400 or 1400 mg/kg/day tetrachloroethylene in drinking water to groups of 20 male and 20 female Sprague-Dawley rats for 90 consecutive days. Body weights were decreased, and relative liver and kidney weights were increased at the higher two doses. 5'-Nucleotidase activity was elevated in a dose-related manner, which indicated possible hepatotoxicity; however, other serum indicators of hepatotoxicity were unaffected. There were no effects on hematological, clinical chemistry or urinalysis parameters, or on gross appearance of tissues.

Groups of male Swiss-Cox mice were administered tetrachloroethylene (>99% pure) in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1000, 1500 or 2000 mg/kg on 5 days/week for 6 weeks (Buben and O'Flaherty, 1985). Group sizes were 26 (0 ppm), 13-19 (100-1000 ppm), and 6 (1500 and 2000 ppm). Four parameters of hepatotoxicity were evaluated at all dose levels: relative liver weight, triglycerides, glucose-6-phosphatase (G6P) activity and SGPT activity. There were no effects on these parameters at 20 mg/kg. Liver weight and triglycerides were significantly increased at $\geq$100 mg/kg and G6P was significantly decreased and SGPT was significantly increased at $\geq$500 mg/kg. The effects were nearly all dose-dependent although liver triglycerides peaked and SGPT levels plateaued at 1000 mg/kg. Histological examination of livers from mice in the 200 and 1000 mg/kg dose groups showed severe degenerative changes with evidence of karyorrhexis (nuclear disintegration); centrilobular necrosis occurred in some of the livers at 1000 mg/kg. Plots of the heptotoxicity parameters against total urinary metabolites were linear in all cases, suggesting that the hepatotoxicity is directly related to the degree of tetrachloroethylene metabolism.

3.1.2. Inhalation. The effects of subchronic inhalation exposure to tetrachloroethylene have been examined in rats, mice, rabbits, guinea pigs and monkeys. These effects are summarized in Table 3-1.

Carpenter (1937) exposed three groups of albino rats to tetrachloroethylene vapors at average concentration levels of 70, 230 or 470 ppm, 8 hours/day, 5 days/week for 7 months. The control group consisted of 18 unexposed rats. After exposure and a 46-day recovery period, rats exposed to 470 ppm tetrachloroethylene had cloudy and congested livers with swelling but no evidence of fatty degeneration or necrosis, increased renal secretion with cloudy swelling and desquamation of kidneys, and congested spleens with increased pigment. Following exposure to 230 ppm tetrachloroethylene and a 20-day recovery period, treated rats had similar but less severe pathologic changes than the highest exposure group. These changes included renal and splenic congestion and reduced hepatic glycogen storage. There was no evidence of pathologic changes in the liver, kidneys or spleen of rats exposed to 70 ppm tetrachloroethylene for 7 months, and apparently sacrificed without a recovery period. Upon microscopic examination of rats at each exposure level, Carpenter (1937) did not observe pathologic changes in the heart, brain, eyes or nerve tissue. Functional parameters (icteric index, Van den Bergh test for bilirubin, blood and urinalysis) were normal at all exposure levels. The fertility index (actual number of litters/possible number of litters) was increased for female rats exposed 150 times to 230 or 470 ppm tetrachloroethylene. A NOEL of 70 ppm tetrachloroethylene for rats can be estimated from this study.

Rowe et al. (1952) exposed rats, rabbits, guinea pigs and monkeys to tetrachloroethylene vapors at levels of 100-400 ppm, 7 hours/day, 5 days/week for ~6 months. No abnormal growth, organ function or histopathologic

TABLE 3-1

Effects of Subchronic Inhalation Exposure to Tetrachloroethylene in Animals

Species	Dose/ Concentration (ppm)	Exposure Period	Effects	Reference
Rats	15	4 hours/day for 5 months	EEG changes and protoplasmal swelling of cerebral cortical cells, some vacuolated cells and signs of karyolysis.	Dmitrieva, 1966
Rats	70, 230 or 470	8 hours/day, 5 days/week for 150 exposures (7 months)	70 ppm: No pathological findings. 230 ppm: Similar, but less severe pathological findings as with higher dose; congestion and light granular swelling of kidneys. 470 ppm: Congested livers with cloudy swelling; no evidence of fatty degeneration or necrosis; evidence of kidney injury including increased secretion, cloudy swelling and desquamation; congestion of spleen.	Carpenter, 1937
Rats	100-400	7 hours/day, 5 days/week for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952
Rats	100-1600	6 hours/day, 5 days/week for 13 weeks	Mortality at 1600 ppm, hepatic congestion at 200-800 ppm	NTP, 1986

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TABLE 3-1 (cont.)

Species	Dose/ Concentration (ppm)	Exposure Period	Effects	Reference
Mice	15-74	5 hours/day for 3 months	Decreased electroconductance of muscle and "amplitude" of muscular contraction.	Dmitrieva, 1968
Mice	100-1600	6 hours/day, 5 days/week for 13 weeks	Mortality at 1600 ppm, liver necrosis at 400-1600 ppm.	NTP, 1986
Gerbils	120	continuously for 12 months	Decreased taurine content in hippocampus and posterior cerebellar vermis and increased glutamine content in the hippocampus.	Briving et al., 1986
Gerbils	120	continuously for 12 months	Alteration in the fatty acid composition of cerebral cortea and hippocampus phospholipids.	Kyrklund et al., 1984
Mice	9-150	continuously for 30 days	Abnormal gross liver appearance $\geq$9 ppm, increased liver weight $\geq$9 ppm, increased BuChe $\geq$37 ppm, altered liver histopathology $\geq$9 ppm.	Kjellstrand et al., 1984
Rabbits	15	3-4 hours/day for 7-11 months	Depressed agglutinin formation.	Mazza, 1972
Rabbits	15	3-4 hours/day for 7-11 months	Moderately increased urinary urobilinogen, pathomorphological changes in the parenchyma of liver and kidneys.	Navrotskii et al., 1971

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TABLE 3-1 (cont.)

Species	Dose/ Concentration (ppm)	Exposure Period	Effects	Reference
Rabbits	100-400	7 hours/day, 5 days/week for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952
Guinea pigs	0, 100, 200 or 400	7 hours/day, 5 days/week for 132 or 169 exposures	100 ppm: Increased liver weights in females; fat vacuoles in livers of both sexes. 200 ppm: Increased liver weights with some fatty degeneration in both sexes; slight increase in hepatic lipid content; several small fat vacuoles in liver. 400 ppm: More pronounced liver changes than at 200 ppm; cirrhosis; increased liver weight; increase in neutral fat and esterified cholesterol in the liver; moderate central fatty degeneration.	Rowe et al., 1952
Monkeys	100-400	7 hours/day, 5 days/week for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952
Gerbils	0, 60 or 320	continuous for 3 months	≥60 ppm: Decreased DNA concentration in frontal cerebral cortex. 320 ppm: Decreased frontal cortical wet weight, altered S-100, DNA and protein concentrations in various regions of the brain.	Rosengren et al., 1986

findings were seen at any exposure level among treated rats, rabbits or monkeys. Guinea pigs, however, were more susceptible to tetrachloroethylene, with adverse effects occurring at all exposure levels. Female guinea pigs exposed to tetrachloroethylene vapors at a level of 100 ppm had increased liver weights, while both sexes of guinea pigs exposed to 200 ppm had increased liver weights with some fatty degeneration, a slight increase in hepatic lipid content, and the presence of several small hepatic fat vacuoles. Guinea pigs exposed to the highest exposure level used in this study (400 ppm tetrachloroethylene) had more pronounced liver changes than at the 200 ppm exposure level, including cirrhosis, increased liver weight, increased hepatic neutral fat and esterified cholesterol, and moderate hepatic central fatty degeneration. A LOAEL of 100 ppm tetrachloroethylene for hepatic effects in guinea pigs can be derived from this study. Rowe et al. (1952) reported no histopathologic lesions of the brains of any species at any concentration. It is unclear from what animals brains were taken for examination.

NTP (1986) conducted preliminary 13-week studies where rats and mice were exposed to 100-1600 ppm tetrachloroethylene, 6 hours/day, 5 days/week. Tetrachloroethylene caused 20-70% mortality in both species at the highest dose. At 200-800 ppm, minimal to mild hepatic congestion occurred in rats. In mice, 1600 ppm caused mortality, and 400-1600 ppm produced minimal to mild hepatic leukocytic infiltration, centrilobular necrosis and bile stasis. Mitotic alteration in the liver occurred at $\geq$200 ppm and minimal renal cell karyomegaly occurred at $\geq$400 ppm. No adverse effects were noted in rats or mice at 100 ppm.

Four studies from the foreign literature (Dmitrieva, 1966, 1968; Mazza, 1972; Navrotskii et al., 1971) of subchronic inhalation exposure to tetra-

chloroethylene were summarized by U.S. EPA (1985a). EEG changes and protoplasmal swelling of cerebral cortical cells, and the presence of some vacuolated cells and signs of karyolysis were reported in the brains of rats exposed to 15 ppm tetrachloroethylene vapors, 4 hours/day for 5 months (Dmitrieva, 1966). Mice exposed to 15-74 ppm tetrachloroethylene for 5 hours/day for 3 months reportedly had decreased electroconductance of muscle and "amplitude" of muscular contraction (Dmitrieva, 1968). Rabbits exposed to tetrachloroethylene vapors at a level of 15 ppm for 3-4 hours/day for 7-11 months had depressed agglutinin formation (Mazza, 1972), and moderately increased urinary urobilinogen and pathomorphological changes in hepatic and renal parenchyma (Navrotskii et al., 1971). The lack of further details and dose-response data in these four studies and the lack of similar observations in several well conducted domestic experiments precludes their use for quantitative human risk assessment for inhalation exposure to tetrachloroethylene.

Rosengren et al. (1986) exposed groups of four male and four female Mongolian gerbils to 60 or 320 ppm (407 or 2170 mg/m^3) continuously for 3 months to determine effects on subtle biochemical parameters of the brain. A control group of eight males and eight females was maintained. The only effect observed at 60 ppm was decreased concentration of DNA in the frontal cerebral cortex. At 320 ppm, there was a significant reduction in the wet weight of the cerebral cortex and alterations in the concentrations of S-100, DNA and protein in several regions of the brain. According to the investigators, these observations suggested that tetrachloroethylene caused frontal cortical atrophy and affected the astroglial cells of several regions of the brain.

Brain amino acid and glutathione concentrations were determined in groups of six Mongolian gerbils (3/sex) that were exposed to 0 or 120 ppm tetrachloroethylene continuously for 12 months (Briving et al., 1986). Treatment-related effects included decreased taurine content in the hippocampus and posterior part of the cerebellar vermis and increased glutamine content in the hippocampus. Uptake of glutamate and gamma-aminobutyric acid (GABA) into the cerebellum and hippocampus was unaffected.

Continuous exposure of six male Mongolian gerbils to 120 ppm tetrachloroethylene for 12 months also caused an alteration in the fatty acid composition of a phospholipid (phosphatidylethanolamine) in the cerevral cortex and hippocampus (Kyrklund et al., 1984).

Liver weight, liver pathology, and plasma butyrylcholinesterase (BuChe) activity were evaluated in groups of 30 NMRI mice of each sex that were exposed to 0, 9, 37, 75 or 150 ppm tetrachloroethylene continuously for 30 days (Kjellstrand et al., 1984). Treatment-related effects included abnormal gross pathological appearance at $\geq$9 ppm, significantly increased liver weight at $\geq$9 ppm and significantly increased BuChe activity at $\geq$37 ppm. Gross pathological alterations included enlargement and yellowish coloration. Histological examination revealed enlargement and vacuolization of hepatocytes from all areas of the liver but normal trabecular arrangement. Although the pathologic alterations were observed at the 9 ppm exposure concentration, they were most pronounced above 75 ppm. Increased liver weight and serum BuChe activity also occurred in mice that were exposed continuously to 150 ppm tetrachloroethylene for 4, 8 or 14 days, and intermittently to tetrachloroethylene at a time-weighted average concentration of 150 ppm for 30 days. Liver weights were still increased (10%)

120 days following 30 days of continuous exposure to 150 ppm. It should be noted that the significance of increased serum BuChe activity in this study is unclear because there was wide variability in BuChe activity in the controls and because serum BuChe can be modulated by nonhepatic factors (Kjellstrand et al., 1984).

3.2. CHRONIC

3.2.1. Oral. The only source of information regarding chronic oral toxicity resulting from exposure to tetrachloroethylene is the NCI (1977) carcinogenicity bioassay with Osborne-Mendel rats and B6C3F1 mice. Groups of 50 male and 50 female rats and equal numbers of mice received various levels of tetrachloroethylene in corn oil by gavage, 5 days/week for 78 weeks. TWA doses for this study were 450 and 550 mg/kg/day for male mice, 300 and 400 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats. Control groups consisted of 20 male and 20 female animals of each species that were untreated and equal numbers of vehicle-treated animals. Toxic nephropathy was observed at all dose levels in both sexes of mice and rats.

3.2.2. Inhalation. Pegg et al. (1978) reported the results of a disposition study in Sprague-Dawley rats following inhalation exposure to tetrachloroethylene at a level of 4 g/m^3 (600 ppm), 6 hours/day, 5 days/week for 12 months. Unspecified reversible liver damage was observed in the treated rats.

In a 2-year NTP (1986) inhalation study, groups of 50 male and 50 female F344/N rats were exposed to 0, 200 or 400 ppm and 50 male and 50 female B6C3F1 mice were exposed to 0, 100 or 200 ppm; both species were exposed 6 hours/day, 5 days/week for 103 weeks. Exposure had no effect on body weights, but survival of high-dose male rats, high-dose mice of both sexes,

and low-dose male mice (at 74 weeks) was significantly less than controls after ≥74 weeks of exposure. Reduced survival was attributed by NTP (1986) possibly to the development of mononuclear cell leukemia in rats and hepatocellular carcinomas in mice. Nonneoplastic lesions were restricted to the kidney and in rats consisted of karyomegaly in all exposed groups and tubular cell hyperplasia in males at 0/49, 3/49 and 5/50 and in females at 0/50, 0/49 and 1/50 in the control, low and high groups, respectively. In mice, tubular cell karyomegaly was observed in all exposed groups. Nephsosis was evident in both exposed groups of female mice.

Human health effects as a result of chronic inhalation exposure to various concentrations of tetrachloroethylene include respiratory tract irritation, nausea, headache, sleeplessness, abdominal pains and constipation (Chmielewski et al., 1976; Coler and Rossmiller, 1953; Stewart et al., 1970; von Oettingen, 1964). Liver cirrhosis, hepatitis and nephritis have also been reported (Stewart, 1969). Side effects from the therapeutic use of tetrachloroethylene as an antihelmintic agent also have been reported (von Oettingen, 1964). Lack of dose quantification and a dose-response relationship precludes the use of these human data for quantitative risk assessment for inhalation exposure to tetrachloroethylene.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenicity of tetrachloroethylene following oral administration were not located in the available literature.

3.3.2. Inhalation. Schwetz et al. (1975) exposed 17 pregnant Sprague-Dawley rats and 17 pregnant Swiss-Webster mice to tetrachloroethylene by inhalation at a level of 300 ppm for 7 hours/day on days 6-15 of gestation. Caesarean sections were done on day 18 (mice) or 21 (rats). Rats had a

statistically significant reduction in mean maternal body weight, while mice had increased mean relative maternal liver weight. The fetal body weights of mice were depressed significantly. A significantly increased number of rat fetuses were resorbed. For mice, the incidences of subcutaneous edema, delayed ossification of skull bones and split sternebrae were increased significantly, compared with incidences in control mice.

Carpenter (1937) did not detect any adverse effects on reproductive performance among rats exposed to 70, 230 or 470 ppm tetrachloroethylene, 8 hours/day, 5 days/week for 28 weeks. In an unpublished teratogenicity study reported by U.S. EPA (1985a), Sprague-Dawley rats were exposed to 0 or 300 ppm (2034 mg/m^3) tetrachloroethylene for 7 hours daily (Belles et al., 1980). Additional information regarding experimental design is ambiguous: exposures were 5 days/week (schedule during gestation exposure not specified), 19-24 rats were examined (numbers exposed not specified), one-half of the rats were exposed for 3 weeks prior to mating, and all rats were exposed during gestation on days 0-18 or 6-18 (numbers exposed or examined in each group not specified). Concentrations in the exposure chamber either fluctuated or were higher than intended as measurements taken 15 minutes before the end of exposure showed 568 ppm. Treatment-related effects reportedly included maternal ataxia, loss of balance and death during pregestational exposure, decreased maternal weight gain, and increased maternal absolute (not relative) liver and kidney weights, and unspecified fetal skeletal ossification anomalies. Teratogenic or additional embryotoxic effects were not observed.

In an associated study, Hardin et al. (1981) exposed Sprague-Dawley rats to 500 ppm tetrachloroethylene for 6-7 hours/day on gestational days 1-19. It is stated that the target number of litters per group was 30; however,

the actual numbers were not given. Tetrachloroethylene was scored negative for maternal toxicity, fetal toxicity, and teratogenicity (actual data not reported). The brevity of result and protocol reporting makes this study difficult to interpret.

In the same paper, results of exposure of rabbits to 500 ppm tetrachloroethylene for 6-7 hours/day on days 1-24 of gestation are also discussed. The target number of litters/group was given as 20 (actual numbers not reported). Again, tetrachloroethylene was scored negative for maternal toxicity, fetal toxicity, and teratogenicity.

In a behavioral teratology study, groups of 13-21 Sprague-Dawley rats were exposed for 7 hours/day to 0 or 100 ppm terachloroethylene on days 14-20 of gestation, 0 or 900 ppm terachloroethylene on days 14-20 of gestation, and 0 or 900 ppm terachloroethylene on days 7-13 of gestation (Nelson et al., 1980). Seven behavioral tests were used to evaluate effects at several stages of development (postnatal days 4-46); one male and one female from each litter were used for each test. Neurochemical analyses of whole brains except cerebellum and histological examination of brains were conducted on pups at 0 or 21 days of age. Effects were not associated with 100 ppm treatment. Effects occurred in rats exposed to 900 ppm including reduced maternal feed consumption and weight gain without liver or kidney histological alterations, and decreased performance of pups exposed on gestation days 7-13 on the tests of neuromuscular ability (ascent and rotorod) on certain days of testing. Offspring from dams exposed on days 14-20 also performed poorly on the ascent test on one test day, but later in development performance was superior to controls and activity was increased in the open field test. The neurochemical analyses showed, for the

21-day-old offspring, decreases in dopamine in those exposed on gestation days 14-20 and decreases in acetylcholine in those exposed on days 7-13 or 14-20.

Additional developmental testing of rats exposed to high concentrations of tetrachloroethylene has been conducted. In an unpublished study reported by U.S. EPA (1985a), Long-Evans hooded rats were exposed to 0 or 1000 ppm (6780 mg/m^3) tetrachloroethylene for 6 hours/day, 5 days/week for 2 weeks before mating through gestation day 20 or on days 0-20 of gestation (Tepe et al., 1982; Manson et al., 1982). Treatment-related effects included increased maternal liver weight, reduced fetal body weight, increased unspecified skeletal and soft-tissue anomalies indicative of embryotoxicity. Neurobehavioral testing of offspring at 10-170 days of age was unremarkable. In a pilot study to the Nelson et al. (1980) behavioral teratology study, exposure of Sprague-Dawley rats to 900 ppm tetrachloroethylene (schedule not specified) on days 7-13 or 14-20 of gestation did not produce fetal external or skeletal malformations.

3.3.3. Oral.

3.3.3.1. **HUMAN STUDIES** -- Information regarding the developmental effects of ingested terachloroethylene in humans was not located in the available literature.

3.3.3.2. **ANIMAL STUDIES** -- Information regarding the developmental effects of orally administered terachloroethylene in animals was not located in the available literature.

3.3.4. Dermal.

3.3.4.1. **HUMAN STUDIES** -- Information regarding the developmental effects of dermally applied terachloroethylene in humans was not located in the available literature.

3.4. TOXICANT INTERACTIONS

Compounds that alter the functional activity of microsomal enzyme systems may affect the toxicity of tetrachloroethylene because it is metabolized by mixed function oxidases (U.S. EPA, 1980a). Phenobarbital pretreatment, however, did not modify the acute hepatotoxicity of tetrachloroethylene (Cornish et al., 1973, 1977). Induction of mixed function oxidases by pretreatment with Aroclor 1254 resulted in altered tetrachloroethylene acute toxicity, manifested by vacuolization of rough endoplasmic reticulum and increased serum glutamate oxaloacetate transaminase activity (Moslen et al., 1977; Reynolds and Moslen, 1977).

Tetrachloroethylene has been associated with intolerance to alcohol, probably because both tetrachloroethylene and alcohol are CNS depressants (Gold, 1969). Synergistic effects, which are identified by lethality as the endpoint, of mixtures of tetrachloroethylene and benzene following intubation to rats have been reported (Withey and Hall, 1975).

Smyth et al. (1969) administered tetrachloroethylene and 26 other solvents in all possible combinations to rats. The results followed a predictive additive toxicity model except for polyethylene glycol 400, butyl ether, dioxane and acetophenone, which had greater than additive toxicity when administered with tetrachloroethylene.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of orally administered tetrachloroethylene to humans were not located in the available literature.

4.1.2. Inhalation. Epidemiologic studies of dry cleaning and laundry workers have determined significant excesses in mortality due to cancers of the lung, cervix, kidney, skin and/or colon (Blair et al., 1979; Kaplan, 1980; Katz and Jowett, 1981; Duh and Asal, 1984; Brown and Kaplan, 1985). Although these studies suggest a possible association between chronic occupational exposure to tetrachloroethylene and increased cancer risk, the evidence must be regarded as inconclusive because the workers were exposed to petroleum solvents and other dry cleaning agents as well as tetrachloroethylene, because other confouding factors such as smoking and low socioeconomic status were not considered in the analyses, because the numbers of site-specific deaths were low and/or because attempts were not made to distinguish between laundry and dry cleaning workers.

The only investigation of dry cleaning workers with no known exposure to petroleum solvents was a subcohort of 615 workers from the Brown and Kaplan (1985) retrospective mortality study. Excess risk for cancer at any site was not identified in the subhcohort. In the entire cohort, which was comprised of 1690 workers with $\geq$23 years of employment and included workers who had potential occupational exposure to petroleum solvents, there were significant excesses of mortality from kidney and bladder cancer (8 cases vs. 2.7 expected; SMR=296) and cancer of the cervix (10 observed vs. 5.1 expected; SMR=296).

Lin and Kessler (1981) did a case-control study of 109 pancreatic cancer cases diagnosed during the period 1971-1975 from 115 hospitals in five metropolitan areas. The control group was composed of subjects who were free from cancer but who were similar to the study group in age (±3 years), sex, race and marital status, and who had been selected at random from among contemporaneous admissions to the same hospital. Cases and controls were asked about demographic characteristics, residential history, toxic exposures, animal contacts, smoking habits, diet, medical history, medications and family history. Males were asked about sexual practices and urogenital conditions. Females were questioned on these topics and also on their marital, obstetric and gynecologic histories. Among other statistically significant associations, an association was found between pancreatic cancer and employment either as a dry cleaner or in a job involving exposure to gasoline. It is not known, however, how many individuals with pancreatic cancer were employed as dry cleaners and how many were employed in occupations involving exposure to gasoline. Furthermore, the dry cleaners may have used a variety of dry cleaning agents other than PCE. Thus this study, although suggestive of an association between employment as a dry cleaner and an excess risk of pancreatic cancer, cannot be said to demonstrate an association between pancreatic cancer and PCE exposure.

4.2. BIOASSAYS

4.2.1. Oral. In an NCI (1977) carcinogenicity bioassay with Osborne-Mendel rats and B6C3F1 mice, groups of 50 male and 50 female rats and equal numbers of mice received various levels of tetrachloroethylene in corn oil by gavage, 5 days/week for 78 weeks. TWA doses for this study were 536 and 1072 mg/kg/day for male mice, 386 and 772 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats.

Control groups consisted of 20 male and 20 female animals of each species that were untreated and equal numbers of vehicle-treated animals. All surviving mice were killed at 90 weeks and all surviving rats at 110 weeks. Decreased survival rates were observed for both species. No increases in tumor incidences were observed for treated rats. Mice, however, had highly significant increases in hepatocellular carcinomas. The incidences of this tumor type in mice were 2/17 untreated control males, 2/20 vehicle control males, 32/49 low-dose males, 27/48 high-dose males, 2/20 untreated control females, 0/20 vehicle control females, 19/48 low-dose females and 19/48 high-dose females. Metastases were reported for one untreated control male, three low-dose males, one low-dose female and one high-dose female.

4.2.2. Inhalation. NTP (1986) conducted 2-year inhalation carcinogenicity studies with F344/N rats and B6C3F1 mice. Groups of 50 males and 50 females were exposed to 0, 200 or 400 ppm (rats) or 0, 100 or 200 ppm (mice), 6 hours/day, 5 days/week for 103 weeks. Survival of high-dose male rats, high-dose female mice and both treated groups of male mice were reduced compared with controls; this was possibly due to mononuclear cell leukemia in rats and hepatocellular carcinomas in mice.

Treated male rats had an increased incidence of mononuclear cell leukemia (control 28/50, low dose 37/50, high dose 37/50). Treated female rats had an increased incidence of leukemia (18/50, 30/50, 25/50) and decreased time to occurrence of the disease. Tetrachloroethylene was also associated with renal tubular cell adenomas or adenocarcinomas in male rats (1/49, control; 3/49, low group; 4/50, high group). Although the incidence of renal tubular cell tumors was not statistically significant, these tumors are considered uncommon in untreated male rats.

Tetrachloroethylene was associated with dose-related increases in incidences of hepatocellular adenomas (11/49, 8/49, 18/50) and hepatocellular

carcinomas (7/49, 25/49, 26/50) in male mice and hepatocellular carcinomas in female mice (1/48, 13/50, 36/50) (control, low and high groups, respectively).

NTP (1986) concluded that there was clear evidence of carcinogenicity of tetrachloroethylene for male F344/N rats as indicated by increased incidence of mononuclear cell leukemia and uncommon renal tubular cell neoplasms. There was some evidence of carcinogenicity for female F344/N rats because of increased incidences of mononuclear cell leukemia. There was clear evidence of carcinogenicity for B6C3F1 mice of either sex as shown by increased incidences of hepatocellular adenomas and carcinomas.

Rampy et al. (1977) exposed groups of 96 male and 96 female Sprague-Dawley rats to tetrachloroethylene vapors at levels of 2 or 4 g/m³ (300 or 600 ppm, respectively), 6 hours/day, 5 days/week [illegible] 12 months. There was no statistically significant difference in any tumor incidence between treated and control animals.

Theiss et al. (1977) tested PCE for carcinogenicity in the strain A mouse pulmonary tumor induction system. The test sample, a product of the Aldrich Chemical Company, was reagent grade with a purity exceeding 95-99%. Strain A/St male mice, 6-8 weeks old, were used in this assay. The maximum tolerated dosage, defined as the dosage that five mice tolerated after six intraperitoneal injections over a 2-week period followed by a 4-week observation period, was determined and used in the bioassay. In the main test, 20 mice per treatment group received three intraperitoneal injections of 80, 200 or 400 mg/kg of PCE weekly until total dosages of 1120, 4800, and 9600 mg/kg, respectively, were achieved. Survivors were sacrificed at 24 weeks after the first injection, and the number of surface adenomas was counted. Results were compared with findings in vehicle (tricaprylin) and untreated controls by the Student t test. PCE did not statistically

increase ($p>0.05$) the incidence of pulmonary tumors in this study. This strain was sensitive to the positive control chemical urethane.

U.S. EPA (1985a) concluded that a negative result in this assay is not considered conclusive, since several chemicals known to be carcinogenic in chronic rodent bioassays induce no response in this assay.

The strain A mouse pulmonary tumor assay is relatively insensitive to mouse carcinogens for which the effect is confined to the liver (Theiss et al., 1977). For example, chloroform, 2-chloroethyl ether and hexachlorocyclohexane induce tumors of the liver (not other sites) in mice (NCI, 1976, 1977b; Innes et al., 1969) but were not carcinogenic in the assay by Theiss et al. (1977). The reasons for the negative lung response are not understood, but it may be due to a smaller concentration of activating enzymes in the lung than in the liver.

A carcinogenicity study of purified PCE in ICR/Ha Swiss mice was described by Van Duuren et al. (1979). Maximum tolerated dosages were determined in range-finding studies 6-8 weeks in duration, and were selected as dosages that did not affect body weight gain or produce clinical signs of toxicity. This study included the following experiments: 1) 30 females were treated topically on the dorsal skin with a single application of 163 mg PCE followed 14 days later by the applications of 5.0 µg phorbol myristate acetate (PMA) to the skin 3 times weekly until termination of the study at 428-576 days; median survival time was 428-576 days. 2) 30 females were given thrice weekly topical applications of 54 mg PCE for the duration of the test (440-594 days), with a median survival time of 317-589 days. A vehicle (acetone) control group of 30 mice and an untreated control group of 100 mice were included in these experiments.

In the initiation-promotion experiment, 210 mice treated with PMA alone were also on test. The mice were 6-8 weeks old at the beginning of the study, and were housed six to a cage. Test sites on the skin were shaved as necessary and were not covered; however, it was the authors' impression that PCE was immediately absorbed and that evaporation from test sites was minimal (Van Duuren, 19__). The animals were weighed monthly and each animal was examined by necropsy. Tumors and lesions as well as skin, liver, stomach and kidneys were examined histologically.

PCE did not show initiating activity in the initiation-promotion experiment; the number of mice with skin papillomas (squamous cell carcinomas) was: 4 (0) initiated with PCE, 15 (3) treated with PMA alone, and 0 (0) in the control groups. The study involving repeated application to the skin produced lung and stomach tumors in 16 and 0 PCE-treated mice, 11 and 2 vehicle-treated controls, and 30 and 5 untreated controls, respectively.

U.S. EPA (1985a) concludes that the negative results for PCE in mouse skin as an initiator and as a complete carcinogen can be reconciled with the positive mouse liver response in the NCI study if it is hypothesized that the skin does not have the necessary enzymes to convert PCE to an active metabolite, whereas the liver does have this capability.

The lack of sensitivity of skin application test, as compared with tests using other routes of exposure, is apparent from the results of Van Duuren et al. (1979) with 1-chloroprene, cis-1,3-dichloropropene and 2-chloropropanal. They found that none of the three compounds induced a response as initiators in initiation-promotion experiments or with repeated topical application on the skin. However, they did observe a statistically significant increase in the incidence of forestomach tumors in female Ha:ICR

Swiss mice dosed by gavage with 1-chloroprene ($p<0.0005$) and 2-chloroproponal ($p<0.05$) and in the incidence of local sarcomas in female Ha:ICR Swiss mice treated with cis-1,3-dichloropropene ($p<0.0005$) by subcutaneous injection.

4.2.3. Selected Pharmacokinetics Relevant to Interspecies Extrapolation. U.S. EPA (1985a) evaluated the pharmacokinetics of tetrachloroethylene relevant to interspecies dose-response extrapolation; the material in this section is taken from U.S. EPA (1985a). It is generally recognized that the carcinogenicity of the chlorinated ethylenes relates to their metabolic conversion to biologically reactive intermediates. The metabolism of tetrachloroethylene has been investigated in mice, rats and humans. In general, the end metabolites have been poorly characterized in these species, but there is no experimental evidence that indicates qualitative differences in metabolic pathways.

Pharmacokinetic/metabolic evaluations following oral exposure considered most relevant to species extrapolation include Pegg et al. (1979), Schumann et al. (1980), and Buben and O'Flaherty (1985).

Pegg et al. (1979) and Schumann et al. (1980) administered ^{14}C-tetrachloroethylene in corn oil to Sprague-Dawley rats and B6C3F1 mice as single intragastric doses of 1 or 500 mg/kg. ^{14}C radioactivity was measured in exhaled breath, urine, feces and carcass for 72 hours following dosing. In addition, pulmonary excretion of parent compound was monitored. The results of these investigations are shown in Table 4-1.

For rats, 29 and 10% of the 1 and 500 mg/kg doses, respectively, were metabolized, which indicated that metabolism was both limited and saturable. In mice given 500 mg/kg, 17% of the dose was metabolized.

TABLE 4-1

Disposition of ^{14}C-Tetrachloroethylene Radioactivity for 72 Hours After Single Oral Doses to Sprague-Dawley Rats and B6C3F1 Mice[a]

	Rats[b,c]		Mice[b,c]
	1 mg/kg bw (0.25 mg/kg/animal)	500 mg/kg bw (125 mg/animal)	500 mg/kg bw (12.25 mg/animal)
Disposition of radioactivity[d]			
Expired unchanged	0.174 (71%)	110.67 (90%)	8.90 (83%)
Metabolized			
$^{14}CO_2$	0.007	0.57	0.14
Urine	0.040	5.72	1.53
Feces	0.015	4.82	0.13
Carcass	0.008	1.41	0.05
Total metabolized	0.070 (29%)	12.52 (10%)	1.85 (17%)
Total recovered	0.244	123.19	10.75

[a]Source: U.S. EPA, 1985a

[b]Based on average experimental animal weight: 250 g, rat; 24.5 g, mouse

[c]Average of 3

[d]Disposition of radioactivity expressed as mg-equivalent per animal

Buben and O'Flaherty (1985) examined tetrachloroethylene metabolism in male mice dosed 5 days/week for 6 weeks by gavage using a corn oil vehicle. They found that metabolism was both saturable and dose-dependent. Metabolism was evaluated based on the level of urinary TCA. U.S. EPA (1985a) judged that urinary TCA is expected to represent 70-80% of total tetrachloroethylene metabolized. The data from this study are shown in Figure 4-1. Comparison of the amount metabolized from the Schumann et al. (1980) and Pegg et al. (1979) studies, where mice were given 500 mg/kg to the amount metabolized for a 500 mg/kg dose based on Figure 4-1, indicates good agreement between the two studies. The molar equivalent metabolized dose from Figure 4-1 (367 μmol) represents 80% of the molar equivalent metabolized dose (455 μmol) from Schumann et al. (1980) and Pegg et al. (1979).

4.3. OTHER RELEVANT DATA

Tetrachloroethylene elicited a positive response in the Salmonella typhimurium reverse mutation assay and the host-mediated assay with mice and using S. typhimurium (Cerna and Kypenova, 1977). Tetrachloroethylene was negative in forward mutation assays with Escherichia coli (Greim et al., 1975) and failed to induce chromosomal aberrations in bone marrow cells of mice that received 1 or 5 daily intraperitoneal injections of the compound (Cerna and Kypenova, 1977).

4.4. WEIGHT OF EVIDENCE

IARC (1979) concluded that there was limited evidence that tetrachloroethylene is carcinogenic in mice, based on the increased incidence of hepatocellular carcinomas in both sexes of mice following oral administration (NCI, 1977). Recent inhalation studies with rats and mice (NTP, 1986) indicate that tetrachloroethylene is also carcinogenic by this route.

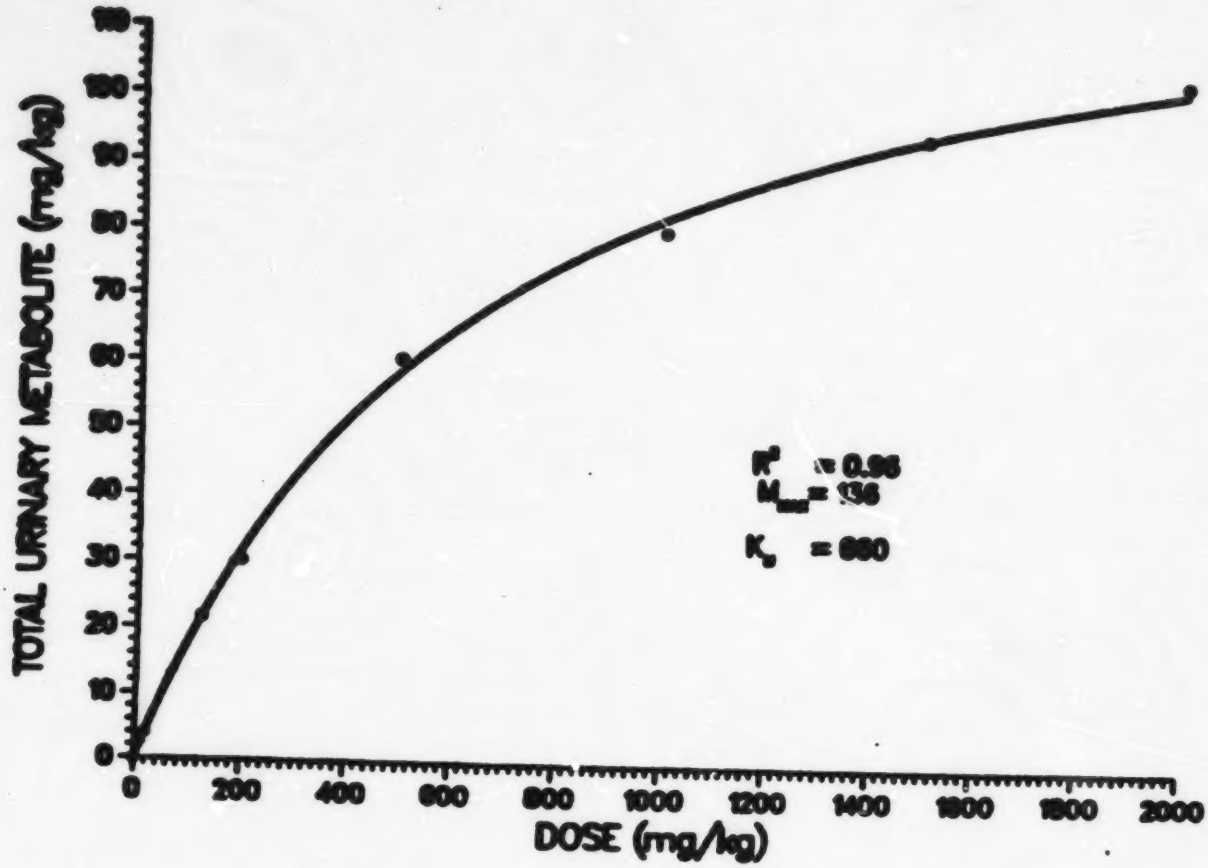

FIGURE 4-1

Relationship Between the Tetrachloroethyle Dose and the Amount of Total Urinary Metabolite Excreted per Day by Mice in Each Group

Source: U.S. EPA, 1985a

Human carcinogenicity data, consisting of a proportionate mortality study of 330 former laundry workers, was considered to be inadequate for assessing human cancer risk associated with exposure to tetrachloroethylene (IARC, 1982). Likewise, the evidence for tetrachloroethylene activity in short-term tests was considered inadequate (IARC, 1982). Applying the criteria of the U.S. EPA (1986b) Carcinogen Assessment Guidelines for evaluating the overall weight of evidence of carcinogenicity to humans, tetrachloroethylene has been tentatively designated in weight of evidence Group B2 - Probable Human Carcinogen (U.S. EPA, 1986c). This conclusion has not yet been formalized or "verified" by EPA pending a dialog between the agency and its science advisory board.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1986a,b) recommended a TWA-TLV of 50 ppm (335 mg/m^3) and an STEL of 200 ppm (1340 mg/m^3) to prevent discomfort and subjective complaints associated with prolonged exposure to 100-200 ppm. U.S. EPA (1980a) recommended an ambient water quality criterion of 8.0 µg/ℓ associated with a cancer risk of 10^{-5} assuming daily consumption of 2 ℓ water and 6.5 g contaminated aquatic organisms. An RfD of $1x10^{-2}$ mg/kg/day, based on the rat oral gavage study by Buben and O'Flaherty (1985) is presented in IRIS (U.S. EPA, 1987) as a verified RfD.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Tetrachloroethylene is a chemical that has been demonstrated to be carcinogenic in animals, and for which data are sufficient for estimation of carcinogenic potency. For the purposes of this document series, RfDs are not estimated for compounds for which quantitative risk assessment based upon cancer is conducted.

6.2. REFERENCE DOSE (RfD)

Tetrachloroethylene is a chemical that has been demonstrated to be carcinogenic in animals, and for which data are sufficient for estimation of carcinogenic potency. For the purposes of this document series RfDs are not calculated when positive cancer data are available.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. From the data of Buben and O'Flaherty (1985), U.S. EPA (1985a) estimated the quantity of metabolites that contributed to the carcinogenic response for the NCI (1977) study with B6C3F1 mice.

Potency estimates expressed in terms of both metabolized and administered dose are shown in Table 6-1. Potency in terms of administered dose (A) was calculated from potency in terms of metabolized dose (M) by using the relationship M=0.2A. This relationship was estimated by U.S. EPA (1985a) and based on the data of Buben and O'Flaherty (1985). For comparative purposes, potency was also calculated using metabolized dose estimated from the data of Schumann et al. (1980); the estimates generated by the two methods were similar. U.S. EPA (1985a) recommended that the slope estimate calculated from tumor incidence in female mice, 5.1×10^{-2} $(mg/kg/day)^{-1}$, be used to represent the potency of tetrachloroethylene

TABLE 6-1

Dose Response Data and Potency (Slope) Estimates[a]

Group	Animal TWA Metabolized Dose (mg/kg/day)[b]	Tumor Incidence[c]	Human Potency Estimate in Terms of Metabolized Dose $(mg/kg/day)^{-1}$	Human Potency Estimate in Terms of Administered Dose[d] $(mg/kg/day)^{-1}$
Male	0	2/20	3.4×10^{-1}	6.8×10^{-2}
	37.73	32/48		
	52.11	27/45		
Female	0	0/20	2.5×10^{-2}	5.1×10^{-2}
	31.07	19/48		
	45.39	19/45		

[a] Source: U.S. EPA, 1985a

[b] Calculated from metabolized dose data shown in Table 4-1 by multiplying by 78 weeks/90 weeks and 5 days/7 days

[c] The denominators are the number of animals that survived at the time the first hepatocellular carcinoma occurred in each study

[d] Human potency estimates were calculated from animal potency estimates by multiplying by $(weight_{human}/weight_{animal})^{1/3}$

because the data showed a clearer dose-response than for male mice. The slope calculated on the basis of male mice was 6.8×10^{-2} $(mg/kg/day)^{-1}$, which is consistent and supports that calculated from the female mouse data.

6.3.2. Inhalation. In the only inhalation cancer bioassay available to U.S. EPA (1985a), Rampy et al. (1977) did not find any statistically significant difference in any tumor incidence between control rats and those exposed to tetrachloroethylene vapors at levels of 2 or 4 g/m^3 (300 or 600 ppm, respectively), 6 hours/day, 5 days/week for 12 months. U.S. EPA (1985a) calculated unit risks for inhalation exposure using a variety of pharmacokinetic approaches for route extrapolation. The unit risk of 4.8×10^{-7} $(\mu g/m^3)^{-1}$ was recommended for use as the representative estimate. The estimate was based upon the relationship between exposure concentration and tetrachloroethylene metabolites in urine from the human data of Bolanowska and Golacka (1972). In this study, five subjects were exposed to 390,000 $\mu g/m^3$ tetrachloroethylene for 6 hours. Metabolites in the urine were monitored for 20 hours. The quantity of metabolites for the time period from the end of exposure up to 20 hours was taken directly from the experimental data. The remainder of the area under the curve, 20 hours to infinity, was estimated as follows:

$$Cxt^{1/2}/0.693$$

where:

C = concentration of metabolites at the last sampling time
$t^{1/2}$ = assumed to be 100 hours

Assuming that at low exposure concentrations, below those saturating metabolism that the amount metabolized is linearly related to the air concentration and the duration of exposure, the amount metabolized associated with 1 $\mu g/m^3$ of tetrachloroethylene in air is:

$$(13 \text{ mg}/39{,}000 \text{ mg}/m^3) \times (24 \text{ hours}/6 \text{ hours}) = 1.33 \times 10^{-4} \text{ mg/day}$$

or

$$1.9 \times 10^{-6} \text{ mg metabolites/kg/day/1 } \mu g/m^3 \text{ exposure}$$

The cancer risk associated with exposure to 1 $\mu g/m^3$ tetrachloroethylene is as follows (see Table 6-2):

$$2.5 \times 10^{-1} \text{ risk } (\text{mg metabolites/kg/day})^{-1} \times 1.9 \times 10^{-6} \text{ mg metabolites produced/kg/day/1 } \mu g/m^3 = 4.8 \times 10^{-7} (\mu g/m^3)^{-1}$$

More recently, U.S. EPA (1986a) has updated its dose-response analysis by using the results of the NTP (1986) bioassay with rats and mice as the basis for carcinogenicity risk analysis for inhalation exposure to tetrachloroethylene. Six sets of tumor incidence data were used: mononuclear cell leukemia in male and female rats, liver carcinomas in male and female mice, and combined incidences of liver adenomas and carcinomas in male and female mice. The doses used in the NTP (1986) study were converted to metabolized doses using a dose-metabolism relationship described in U.S. EPA (1986a). These data are presented in Tables 6-2 and 6-3. The metabolized dose is expressed as $mg/W^{2/3}/day$, which represents the metabolized dose per body surface area that is assumed to be equally potent (equivalent) among species. The carcinogenic potency (slope) estimates were calculated using the multistage model with these equivalent doses and corresponding tumor incidence data. The slope estimates calculated for the six data sets are presented in Table 6-4 and range from 3.64×10^{-2} $(mg/W^{2/3}/day)^{-1}$ to 1.21×10^{-1} $(mg/W^{2/3}/day)^{-1}$. U.S. EPA (1986a) calculated unit risks ranging from 2.85×10^{-7} to 9.47×10^{-7} for humans exposed to 1 $\mu g/m^3$ in air based on these potency estimates. This range of values is adopted as the estimate of the carcinogenic potency of tetrachloroethylene to humans exposed by inhalation. The methods used to calculate metabolized dose, potency and unit risks are described in detail in U.S. EPA (1986a). The geometric mean of the six unit risk estimates was $5.78 \times 10^{-7} (\mu g/m^3)^{-1}$.

TABLE 6-2

Metabolized Dose and Incidence of Mononuclear Cell Leukemia in Fischer 344 Rats in the NTP (1986) Inhalation Study[a]

Group	Exposure Concentration (ppm)	Human Equivalent Metabolized Dose ($mg/W^{2/3}/day$)[b]	Incidence Rate
Male	0	0	28/50
	200	6.26	37/50
	400	8.45	37/50
Female	0	0	18/50
	200	5.81	30/50
	400	7.84	29/50

[a]Source: U.S. EPA, 1986a

[b]Metabolized dose = M (mg/kg/day) x (5/7) x $W^{1/3}$, where M (mg/kg/day) is the direct estimate of the dose metabolized; the factor 5/7 reflects that animals were exposed only 5 days/week; and W (body weight) = 0.40 kg for male rats and 0.32 kg for female rats. For convenience, the notation $mg/W^{2/3}$ is used to indicate the amount metabolized in terms of mg per two-thirds of body weight, which is assumed to be proportional to the body surface area.

TABLE 6-3

Metabolized Dose and Incidence of Liver Tumors in Mice in the NTP (1986) Inhalation Study[a]

Group	Exposure Concentration (ppm)	Human Equivalent Metabolized Dose ($mg/W^{2/3}/day$)[b]	Incidence Rate	
			Carcinomas	Adenomas/ Carcinomas
Male	0	0	7/49[c]	16/49
	100	9.37	25/47	31/47
	200	14.21	26/50	40/50
Female	0	0	1/46	4/46
	100	8.92	13/42	17/42
	200	13.52	36/47	38/47

[a]Source: U.S. EPA, 1986a

[b]Metabolized dose = M (mg/kg/day) x (5/7) x $W^{1/3}$, where M (mg/kg/day) is the direct estimate of metabolized dose; 5/7 is a factor to adjust for 5 days exposure in a week; and W (body weight) = 0.0374 kg for male mice and 0.0322 kg for female mice.

[c]Only animals surviving beyond 60 weeks are included in the denominator. The first death from liver tumor occurred at 60 weeks.

TABLE 6-4

Unit Risk Estimates Calculated on the Basis of Different Data Sets from the NTP (1986) Bioassay[a]

Data Set	Risk Due to One Unit ($mg/W^{2/3}$)[b] Metabolized Dose	Risk Due to 1 $\mu g/m^3$ of Tetrachloroethylene in Air
Rat (leukemia):		
Males	1.21×10^{-1}	9.47×10^{-7}
Females	1.01×10^{-1}	7.91×10^{-7}
Mouse (liver carcinomas):		
Males	6.67×10^{-2}	5.22×10^{-7}
Females	3.64×10^{-2}	2.85×10^{-7}
Mouse (liver adenomas/ carcinomas):		
Males	1.08×10^{-1}	8.46×10^{-7}
Females	5.05×10^{-2}	3.95×10^{-7}
Geometric mean:	7.38×10^{-2}	5.78×10^{-7}

[a]Source: U.S. EPA, 1986a

[b]The metabolized dose expressed in $mg/W^{2/3}$ (where W is body weight) is assumed to be equivalent (i.e., equally potent, among species).

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APPENDIX

Summary Table for Tetrachloroethylene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^* or Unit Risk Slope	Reference
Inhalation	rats, mice	5.81-14.21 $mg/M^3)^a/day^a$	leukemia, liver tumors	2.85×10^{-7} $(\mu g/m^3)^{-1}$ to 9.47×10^{-7} $(\mu g/m^3)^{-1}$[b]	NTP, 1986; U.S. EPA, 1986a
Oral	mice	536-1072 mg/kg/day	hepatocellular carcinoma	5.1×10^{-2} $(mg/kg/day)^{-1}$	NCI, 1977; U.S. EPA, 1985a

[a]Expressed as human equivalent metabolized dose as estimated by U.S. EPA (1986a).

[b]Geometric mean of 5.78×10^{-7} $(\mu g/m^3)^{-1}$.

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